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PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT  
(PCT Article 36 and Rule 70)



REC'D 11 APR 2005

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Applicant's or agent's file reference J 10012 PCT	<b>FOR FURTHER ACTION</b> See Notification of Transmittal of International Preliminary Examination Report (Form PCT/PEA/416)	
International application No. PCT/EP 03/10406	International filing date (day/month/year) 18.09.2003	Priority date (day/month/year) 18.09.2002
International Patent Classification (IPC) or both national classification and IPC C07C275/34		
Applicant JERINI AG et al.		

1. This International preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 8 sheets, including this cover sheet.  
  
☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).  
  
 These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:
  - I ☒ Basis of the opinion
  - II ☐ Priority
  - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
  - IV ☒ Lack of unity of invention
  - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
  - VI ☐ Certain documents cited
  - VII ☐ Certain defects in the international application
  - VIII ☐ Certain observations on the international application

Date of submission of the demand  30.03.2004	Date of completion of this report  08.04.2005
Name and mailing address of the international preliminary examining authority:   European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer  Kyriakakou, G  Telephone No. +49 89 2399-7835  

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT**

International application No. **PCT/EP 03/10406**

**I. Basis of the report**

1. With regard to the **elements** of the international application (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17)*):

**Description, Pages**

1-362 as originally filed

**Claims, Numbers**

1-183 as originally filed

**Drawings, Sheets**

1/3-3/3 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

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5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

*(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)*

6. Additional observations, if necessary:

**III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 1-183 (incompletely)

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (specify):

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the said claims Nos. 1-183 (incompletely)

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the Standard.

☐ the computer readable form has not been furnished or does not comply with the Standard.

**IV. Lack of unity of invention**

1. In response to the invitation to restrict or pay additional fees, the applicant has:

☐ restricted the claims.

☐ paid additional fees.

☐ paid additional fees under protest.

☒ neither restricted nor paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

☐ complied with.

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☐ not complied with for the following reasons:

4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:

☒ all parts.

☐ the parts relating to claims Nos. .

**V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Yes: Claims	
	No: Claims	1-146, 148-183
Inventive step (IS)	Yes: Claims	
	No: Claims	1-183
Industrial applicability (IA)	Yes: Claims	1-183
	No: Claims	

2. Citations and explanations

**see separate sheet**

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**Re Item III**

**Non-establishment of opinion with regard to novelty an, inventive step and industrial applicability**

Present claims 1-183 relate to an extremely large number of possible compounds and compositions. In fact, the claims contain so many options, variables and possible permutations that a lack of both clarity and conciseness within the meaning of Article 6 PCT arises to such an extent as to render a meaningful examination of the claims impossible. Support in the meaning of Art. 6 PCT and disclosure within the meaning of Art. 5 PCT is to be found, however, for only a very small proportion of the compounds and compositions claimed. It has to be pointed out that the search has been accordingly limited to those parts of the Application which do appear to be clear, supported and disclosed namely those parts closely related to the examples ie. the compounds of the independent claim 147 where the following restriction has been applied X= -(CRR)-NR-CO-NR-CRR, - (CRR)-NR-CS-NR-(CRR)

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The Applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

Accordingly the present communication is **exclusively based on an examination of the claims 1-183 partially at the light/in the context of the examples with the said restriction.**

**Re Item IV**

**Lack of unity of invention**

This International Authority found multiple inventions in this applications, which are not so linked as to form a single general inventive concept (Rule 13.1 PCT). since they provide 10 alternative solutions to the same problem that could have been achieved separately. Due to the lack of Novelty of some of the compounds (see D1 and D3 claim 1) it is considered that the substances claimed are not so linked together as to form a unitary general inventive concept..

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Only one invention has been searched (see restriction Re item III) Assuming that the request for examination is intended to refer to the invention which has been searched the examination is effected on this subject matter.

**Re Item V**

**Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Reference is made to the following documents:

D1: WO-A-02059080  
D2: WO-A-0244126  
D3: WO-A-0117953  
D4: WO-A-9837882  
D5: US-A-6242468  
D6: US-A-2002049199  
D7: US-A-5744485

**2. Novelty (Art.33(2)PCT)**

2.1 The generically defined compounds of the present application and the generically defined prior art D1 and D3 compounds have a large number of compounds in common. The subject matter of the present claims 1-146 and cannot therefore be considered to be novel. The subject matter of the claims 148-183 on file relates to pharmaceutical composition comprising the generically defined compounds of the said claims 1-146 and their use. The prior art documents D1 and D3 disclose pharmaceutical compositions and their use and are therefore prejudicial to the Novelty of the said claims 148-183 on file. The subsequent examination is valid on the condition that new claims are filed which are allowable and which do not contain known subject matter.

2.2 The claimed compounds are novel over the prior art D2 compounds due to the OR substituent.

2.3 The compounds disclosed in the prior art documents D4-D7 differ in several structural features from the claimed compounds.

**3. inventive step (Art.33(3)PCT)**

3.1 The object of the present application is to provide compounds which are rotamase

inhibitors and they are useful for treating diseases that are associated with activity of a rotamase.

**3.2** The prior art documents D1 and D3 which disclose compounds coming structurally very close with the claimed compounds and having rotamase inhibitory activity are considered to represent the closest state of the art.

**3.3** The application does not contain sufficient experimental data in favour of the alleged pharmacological activity. It is reported in the Description (see pages 299-300)-30) that the rotamase inhibitors according to the present invention exhibit dissociation constants of at most about 10 $\mu$ M more preferably about 1 $\mu$ M, most preferably of at most 100nM. The specific compounds are not structurally defined. Thus these test results do not support the alleged pharmacological activity of all the claimed compounds. It has also to be taken into consideration that a technical effect which justifies the selection of specific compounds must be one which can be fairly assumed to be produced by substantially all the claimed compounds. In the present case if some of the claimed compounds are rotamase inhibitors it cannot be regarded as sufficient evidence that all the claimed compounds possess the said activity. Furthermore the prior art documents D1 and D3 disclose urea derivatives coming structurally very close and having good rotamase inhibitory activity.

In view of the compounds disclosed in the prior art documents and taking into consideration that it is well accepted that the properties of chemical compounds depend largely on their chemical structure, the person skilled in the art looking for further rotamase inhibitors, will primarily consider compounds whose structure comes as close as possible to the substances already known to have similar activity. In view of the above considerations it is evident that a variation of the substituents of the phenyl group can influence only quantitatively the biological activity and lead to more or less potent inhibitors. The further modification of the substituents appears therefore to the person skilled in the art as an obvious alternative to the state of the art. An Inventive step cannot therefore be acknowledged.

### **Re Item VII**

#### **Certain defects in the international application**

- 1.** The extremely wide range of possibilities given for the different substituents make the claims 1-183 on file obscure and difficult to construe. Furthermore it renders the said claims speculative in that their scope embraces compounds not yet explored by the Applicant, the effect of which cannot be readily predetermined or assessed.
- 2.** In Claim 1 the general expressions "alkyl", "substituted", "alkylaryl" "cycloalkyl",

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"alkylcycloalkyl", "aryl", "heteroaryl", "heterocyclyl" are non-limitative and are therefore not regarded as obvious modifications or equivalents of the examples which have been given in the description.